REMARKS

Amendments

Claim 3 is incorporated into claim 1, without prejudice or disclaimer, in order to expedite prosecution, in view of the 112, first paragraph rejection. Hence the cancellation of claims 2-3 as moot. The dependencies of claims 4-6 are corrected accordingly. Claim 1 further recites that the "treatment increases time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone" with basis for this language found in at least claim 13, the Example, page 15, lines 22-28 and in the definition of chemotherapeutic agent on pages 16-17 which includes gemcitabine. Claim 12 has been incorporated into claim 37. In addition, claim 37 has been amended to recite that the antibody is not conjugated with the gemcitabine. Claim 38 is added with the same recitation. Support for this recitation can be found throughout the specification where therapy with a conjugated antibody is shown to be optional. Claim 13 is amended to address the Section 112, second paragraph rejection. In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Section 103 - Baselga II etc

In item 5 of the Office Action, claims 1-9, 12-13 and 34-37 are rejected under 35 USC Section 103(a) as being unpatentable over Baselga *et al. Oncology* 11(3):43-48 (1997) ("Baselga II"), Norton *et al. Seminars in Oncology* 24(4 Suppl 10):S10-3-S10-10 (1997), US Patent No. 5,578,482 (Lippman *et al.*), Hynes *et al. Biochimica et Biophysica Acta* 1198(2-3):165-184 (1994), US Patent No. 5,783,186 (Arakawa *et al.*) in view of Clemons *et al. European Journal of Cancer* 33(13):2171-2182 (1997), Mosconi *et al. European Journal of Cancer* 33(Suppl. 1):S14-S17 (1997), Carmichael *et al. European Journal of Cancer* 33(Suppl. 1):S27-S30 (1997)("Carmichael I"), Carmichael *et al. Journal of Clinical Oncology* 13(11):2731-2736(1995) ("Carmichael II") or Tsai *et al. Cancer Research* 56(4):794-801(1996).

Applicants submit that the invention claimed herein is patentable over the cited art.

First, Applicants will explain how claim 1 is distinguished over the cited references.

Claim 1 herein c ncerns a method for the treatment of a human patient with a

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combination of an anti-ErbB2 antibody and gemcitabine, "wherein the treatment increases time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone."

While the Examiner cites to page 47, column 1 of Baselga II as explaining that the "efficacy of this method is measured by time to disease progression," Applicants submit that this cited portion of Baselga II fails to describe the treatment of claim 1 herein which increases time to disease progression compared to therapy with gemcitabine alone. First, column 1 on page 47 of Baselga II is concerned with doxorubicin and paclitaxel, rather than gemcitabine as in claim 1 herein. Second, Baslega II explains that the "main goal of this study is to determine whether the addition of this anti-HER2 antibody increases the time to disease progression compared with the group of patients treated with antibody alone." (Emphasis added) In other words, Baselga II does not know whether combining antibody with doxorubicin or paclitaxel will actually extend time to disease progression compared to therapy with doxorubicin or paclitaxel alone - this remains to be determined. Clearly then, Baselga II provides absolutely no guidance as to whether treatment as in claim 1 herein with a combination of an anti-ErbB2 antibody and gemcitabine will increase time to disease progression compared to therapy with gemcitabine alone.

On the other hand, the instant application provides the actual data from a Phase III human clinical trial demonstrating that assessment of time to disease progression shows a significant augmentation of the chemotherapeutic effect by Herceptin® (page 47, lines 1-4 of the present application). The application teaches combination with the chemotherapeutic drug, gemcitabine (page 17, line 15).

Hence, Applicants submit that the invention of claim 1 is patentable over the cited art which fails to disclose or suggest the treatment therein which increases time to disease progression, compared to therapy with gemcitabine alone.

Aside from the recitation in claim 1 concerning increasing time to disease progression as discussed above, claim 1 requires that treatment with the combination of the anti-ErbB2 antibody and gemcitabine does not significantly increase overall severe adverse events compared to therapy with gemcitabine alone.

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The phase III human clinical trial results described in the present application demonstrate that, in humans, combining Herceptin® with chemotherapy does not significantly increase overall severe adverse events (page 47, lines 1-4). However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated (page 47, lines 25-27).

Human clinical data has confirmed that the presently claimed combination of an anti-ErbB2 antibody and gemcitabine is safe and effective. See Miller *et al. Oncology* 15(2):38-40 (February, 2001) (of record) which describes preliminary results of a phase II human clinical trial which evaluated the presently claimed gemcitabine and anti-ErbB2 antibody combination with respect to HER2-overexpressing metastatic breast cancer. The combination is well tolerated and appears to be highly active (see abstract of Miller *et al.*). Neither significant cardiac toxicity nor clinical congestive heart failure has been reported to date (1st paragraph in column 1 on page 40 of Miller *et al.*).

On the contrary, the cited prior art fails to provide any guidance as to whether or not the presently claimed combination of an anti-ErbB2 antibody and gemcitabine will significantly increase overall severe adverse events in human patients treated therewith.

In sum then, Applicants submit that claim 1 herein is patentable over the cited art. Reconsideration and withdrawal of the rejection of claim 1 and its dependent claims is respectfully requested in view of the above.

Turning now to independent claim 37, Applicants will now explain how that claim is patentable over the cited art.

Claim 37 states that the effective amount of the combination is lower than the sum of the effective amounts of the anti-ErbB2 antibody and the gemcitabine, when administered individually, as single agents. Thus, claim 37 concerns synergy achieved with the combination. The present specification describes a synergistic combination of an anti-ErbB2 antibody (such as HERCEPTIN®) and gemcitabine. Data published after the filing date has confirmed the synergistic effect. Nagourney *et al. Breast Cancer Res. Treat.* 57:116 (1999), of record, state that Trastuzumab (the generic name for HERCEPTIN®) enhances the activity of gemcitabine. Bunn *et al.* found additive or synergistic effects between HERCEPTIN® and gemcitabine in NSCLC lines that overexpress HER-2. (No synergy or additive effects were seen

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with SCLC.) See Bunn *et al. Proc. Am. Assoc. Canc. Res.* 41:719 (2000). Zinner *et al.* state that HERCEPTIN® has been shown to be synergistic with cisplatin and gemcitibine in HER2 overexpressing NSCLC.

While the Examiner acknowledges at page 13 of the Office Action that "evidence of a greater than expected result may also be shown by demonstrating an effect that is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism")", the Examiner further urges that "the prior art teaches an example of a combination therapy involving an anti-ErbB2 antibody and a chemotherapeutic agent where the effect of the combination of the two treatments was synergistic (Hynes *et al.*, above)."

Applicants submit that Hynes *et al.* fails to indicate that the presently claimed combination of an anti-ErbB2 antibody and gemcitabine will be synergistic as in claim 37. Applicants understand the part of Hynes *et al.* upon which the Office is relying on is top of column 2 on page 178. There, Hynes *et al.* state "Tissue culture studies with monoclonal antibody 4D5, developed by Genentech, demonstrate that it acts synergistically with cisplatin, and suggest that it enhances the chemo-sensitivity of cells by reducing DNA repair." Hence, Hynes *et al.* is concerned with the combination of monoclonal antibody 4D5 and cisplatin, rather than gemcitabine as in claim 37 herein. There is no teaching in Hynes *et al.* as to synergy achieved with the anti-ErbB2 antibody and gemcitabine combination herein. Moreover, since gemcitabine has a "unique mechanism of action" (see, *e.g.*, abstract of Mosconi *et al.*), Hynes *et al.* is not enlightening as to whether the mechanism of action of the 4D5 and cisplatin combination would be relevant to an anti-ErbB2 antibody and gemcitabine combination.

Applicants conclude that claim 37 is patentable over the cited art.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above.

Section 103 - Hudziak etc

In item 6 of the Office Action, claims 1-9 and 37 are rejected under 35 USC Section 103(a) as being unpatentable over US Patent No. 5,770,195 (Hudziak *et al.*), and further in view of Clemons *et al.*, Mosconi *et al.*, Carmichael I, Carmichael II or Tsai *et al.*

The rejection of claim 1 is moot in view of the incorporation of language from

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claim 13, which is not rejected, into claim 1. The rejection of claim 37 is also rendered moot by the incorporation of claim 12, which is not rejected eith r, into that claim.

Reconsideration and withdrawal of the rejection is respectfully requested.

Section 103 - Baselga I etc

In item 7 of the Office Action, claims 1-9, 12-13 and 37 are rejected under 35 USC Section 103(a) as being unpatentable over Baselga *et al. J. Clin. Oncol.* 14(3):737-744 (1996) ("Baselga I"), Clemons *et al.*, Mosconi *et al.*, Carmichael I, Carmichael II or Tsai *et al.* and further in view of Hynes *et al.*

Applicants submit that the invention claimed herein is patentable over the cited art.

First, Applicants will explain how claim 1 is distinguished over the cited references.

Claim 1 herein concerns a method for the treatment of a human patient with a combination of an anti-ErbB2 antibody and gemcitabine, wherein the treatment increases time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone.

Applicants submit that the primary reference, Baselga I, fails to describe the treatment herein with a combination of an anti-ErbB2 antibody and gemcitabine which "increases time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone." Baselga I reports a Phase II clinical study involving administration of an anti-ErbB2 antibody alone, and hence is not informative as to the presently claimed anti-ErbB2 antibody with gemcitabine combination as in claim 1 herein, let alone the impact of that treatment on the time to disease progression or severe adverse events. The other references fails to supply the deficiencies of Baselga I as to the presently claimed combination, the time to disease progression compared to therapy with gemcitabine alone, or the overall severe adverse events resulting from therapy with the combination. Applicants submit that claim 1, and its dependent claims, are patentable over the cited art.

With respect to independent claim 37, Applicants submit that it is also patentable over the cited art.

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Claim 37 states that the effective amount of the combination is lower than the sum of the effective amounts of the anti-ErbB2 antibody and the gemcitabine, when administered individually, as single agents. Thus, claim 37 concerns synergy achieved with the combination.

The Examiner relies on Hynes *et al.* as allegedly teaching that "coadministration of an anti-ErbB2 antibody and a non-anthracycline derivative chemotherapeutic agent produces a synergistic treatment effect." (Office Action at page 9, last paragraph). Applicants believe that the Office is relying on page 178, top column 2 for the above assertion. There, Hynes *et al.* state "Tissue culture studies with monoclonal antibody 4D5, developed by Genentech, demonstrate that it acts synergistically with cisplatin, and suggest that it enhances the chemosensitivity of cells by reducing DNA repair." Hence, Hynes *et al.* is concerned with the combination of monoclonal antibody 4D5 and cisplatin, rather than gemcitabine as in claim 37 herein. There is no teaching in Hynes *et al.* as to synergy achieved with the anti-ErbB2 antibody and gemcitabine combination herein. Moreover, since gemcitabine has a "unique mechanism of action" (see, *e.g.*, abstract of Mosconi *et al.*), Hynes *et al.* is not enlightening as to whether the mechanism of action of the 4D5 and cisplatin combination would be relevant to an anti-ErbB2 antibody and gemcitabine combination.

Applicants submit that claim 37 is patentable over the cited art.

Reconsideration and withdrawal of the Section 103 rejection is earnestly requested in view of the above.

Section 103 - Baselga I, Baselga II etc

In item 8 of the Office Action, claims 1-9, 12-13 and 34-37 are rejected under 35 USC Section 103(a) as being unpatentable over Baselga I, Baselga II, Norton *et al.*, Lippman *et al.*, Hynes *et al.*, Arakawa *et al.*, or Hudziak *et al.* and Clemons *et al.*, Mosconi *et al.*, Carmichael I, Carmichael II or Tsai *et al.* and further in view of Maier *et al. Cancer Research* 51(19):5361-5369 (1991), Lewis *et al. Cancer Immunol. Immunother.* 37:255-263 (1993), Van Moorsel *et al. Seminars in Oncology* 24(2 Suppl. 7):S7-17-S7-23 (1997), or Hansen *et al. Annals of Oncology,* 7 (Suppl. 1):29 (1996).

Applicants have explained above how claims 1 and 37 (and the dependent claims) are patentable over the cited art. Applicants submit that the additional references, Maier *et al.*, Lewis *et al.*, Van Moorsel *et al.* and Hansen *et al.*,

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fail to supply the deficiencies of the other cited art with respect to the anti-ErbB2 antibody and gemcitabine combination in the claims herein, much less the ability of the treatment to increase time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone as in claim 1 herein, or the synergy associated with that selection invention as in claim 37 herein.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above.

Section 103 - Armour and Hudziak

In item 10 of the Office Action, claims 1-9, 12-13 and 37 are rejected under 35 USC Section 103(a) as being unpatentable over US Patent No. 4,994,558 (Armour *et al.*) in view of Hudziak *et al.*

First, in relation to claim 1, Applicants submit that the references do not describe the selection invention therein where an anti-ErbB2 antibody is combined with gemcitabine. Moreover, claim 1 is amended herein to state that the treatment increases time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone, and the Office has failed to demonstrate how that aspect of the presently claimed invention was shown in the cited references. Hence, reconsideration and withdrawal of the rejection as to claim 1 as amended herein, and its dependent claims, is respectfully requested.

With respect to claim 37 herein, that claim now recites that the antibody is not conjugated with the gemcitabine and the effective amount of the combination is lower than the sum of the effective amounts of the anti-ErbB2 antibody and the gemcitabine, when administered individually, as single agents. Applicants submit that the Office has not shown how the prior art described the selection of an anti-ErbB2 antibody and gemcitabine herein, much less the unexpected result that the drugs administered as a combination of two individual agents are synergistic. In Armour *et al.* gemcitabine had to be conjugated to an antibody (other than anti-ErbB2) in order to increase the inhibition of the tumor noted in the paragraph spanning columns 10-11. Hence, claim 37 is patentable over the cited art.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above.

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Serial No.: 09/209,023

Section 112, 2nd paragraph

Claim 13 is rejected as indefinite in that "the time to disease progression" and "the response rate" lack antecedent basis. This rejection is obviated by the amendment of claim 13 herein. Reconsideration and withdrawal of the rejection is respectfully requested.

Section 112, 2nd paragraph

Claims 1, 2, 7-9, 12, and 13 are rejected under 35 USC Section 112, first paragraph as allegedly lacking enablement. This rejection is moot in view of the incorporation of non-rejected claim 3 into claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

IDSs

Applicants note that they do not have initialed PTO-1449 forms for the following IDSs:

- IDS filed 9/6/2001 (citing ref. 159)
- IDS filed 1/31/2002 (citing refs.160-166)
- IDS filed 4/10/2002 (citing refs. 167-168)
- IDS filed 6/3/2002 (citing refs. 65-146)
- IDS filed 6/17/2002 (citing ref. 169)

Applicants would appreciate it if the Examiner could advise whether the IDSs and references are in the PTO file. If not, further copies can be provided.

Applicants believe this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,
GENENTECH, INC.

Date: December 10, 2002

By: _____

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Serial No.: 09/209,023

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the pending claims as follows:

1. (Twice Amended) A method for the treatment of a human patient with a [disorder] cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an anti-ErbB2 antibody and gemcitabine, in the absence of an anthracycline derivative, to the human patient in an amount effective to treat the cancer [disorder], wherein the treatment increases time to disease progression, without increase in overall severe adverse events, compared to therapy with gemcitabine alone.

4. (Amended) The method of claim [3] 1 wherein said cancer is selected from the group consisting of breast cancer, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

5. (Amended) The method of claim [4] 1 wherein said cancer is breast cancer.

6. (Amended) The method of claim [5] 1 wherein said cancer is metastatic breast carcinoma.

13. (Amended) The method of claim 1 wherein efficacy is measured by determining [the] time to disease progression or [the] response rate.

37. (Amended) A method for treating a cancer selected from the group consisting of breast cancer, non-small cell lung cancer, pancreatic cancer and bladder cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an anti-ErbB2 antibody and gemcitabine, in the absence of an anthracycline derivative, to a human patient in an amount effective to treat the cancer, wherein the antibody is not conjugated with the gemcitabine and the effective amount of the combination is lower than the sum of the effective amounts of the anti-ErbB2 antibody and the gemcitabine, when

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administered individually, as single agents.

Please cancel claims 2 and 3, without prejudice or disclaimer.

Please add the following claim:

38. (New) The method of claim 1 wherein the antibody is not conjugated with the gemcitabine.

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Fax No.: (703) 872-9306

FROM: Wendy M. Lee
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RE: U.S. Serial No.: 09/209,023
Our Docket No.: P1256R3

Number of Pages including this cover sheet - 14

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